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(54) Title: THERAPEUTIC AGENT FOR HEART FAILURE

(57) Abstract: It is an object of the present invention to provide an agent effective for preventing and/or treating heart failure and/or cardiac hypertrophy. A preventive and/or therapeutic agent for heart failure and/or cardiac hypertrophy, comprising an angiotensin II receptor antagonist and a matrix metalloproteinase inhibitor.

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Therapeutic agent for heart failure

The present invention relates to a therapeutic agent for heart failure and/or cardiac hypertrophy. More specifically, the present invention relates to a therapeutic agent for heart failure and/or cardiac hypertrophy containing an angiotensin II receptor antagonist and a matrix metalloproteinase inhibitor in combination.

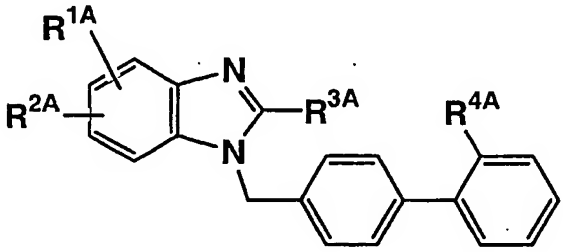
Heart failure is a pathological condition in which normal cardiac output cannot be maintained due to a disorder of the cardiac function. Various diseases such as cardiac infarction, hypertensive heart disease or congestive cardiomyopathy are considered as underlying etiologies for heart failure.

When the cardiac output is decreased by imposing chronic mechanical load on the heart, the heart responds to the condition by causing morphological change such as the enlargement of cardiac ventricles or ventricular hypertrophy such as left ventricular hypertrophy so as to maintain a normal systolic stress at such an acute phase, or by using a compensatory mechanism such as an increase in a sympathetic activity. More specifically, various nervous or humoral factors are recruited against the mechanical load, and protein synthesis by myocardial cells is increased. Moreover, changes in the expression of various genes or the qualitative alteration of non-myocardial cells, such as increased synthesis of an extracellular matrix, are also observed. However, a negative result of the compensatory mechanism against the mechanical load is that as it continues to operate for an extended period of time, it puts a load on the heart. Furthermore, when such a compensatory mechanism is disrupted, the cardiac ventricle of a hypertrophic heart is enlarged, and the cardiac function decreases, thereby resulting in heart failure. Thus, cardiac hypertrophy is considered to be the preliminary stage of heart failure as well as a phenomenon of adaptation to a load. Accordingly, if factors causing the progression of cardiac hypertrophy to heart failure due to a breakup of the compensatory mechanism are clarified at the cellular level, and these factors can be controlled using a pharmaceutical agent, the agent can be used in medical treatment for heart failure.

Presently, the treatment for heart failure is classified into the improvement of pumping action, the reduction of load, and the improvement of edema. A cardiotonic agent, an angiotensin-converting enzyme inhibitor, and a diuretic are used in the above types of treatments, respectively. However, these agents also have problems regarding the margin of safety or adverse drug effects, and these agents are effective in only a statistically limited number of patients. Thus, the conventional agents are not fully satisfactory.

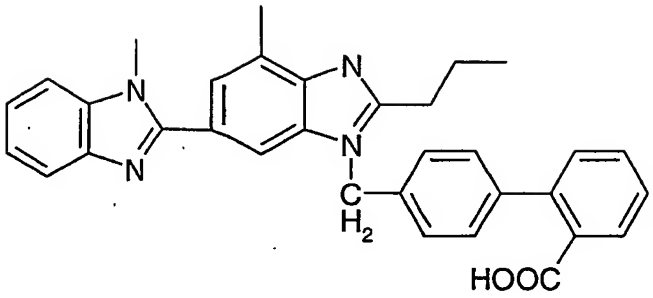
Angiotensin II (hereinafter abbreviated as AII) is a hormone, which is converted from angiotensin I by an angiotensin-converting enzyme in a renin-angiotensin system. This hormone has a strong vasoconstrictor action and is closely associated with the development and maintenance of hypertension or the development and progression of arteriosclerosis. At present, an AII receptor antagonist is used as an agent for treating hypertension, since it prevents the binding of AII to its receptor and suppresses the vasoconstrictor action.

EP-A-502314 corresponding to Japanese Patent Laid-Open No. 4-346978 describes, as a compound with an AII receptor antagonism, benzimidazole derivatives represented by the following general formula (A):



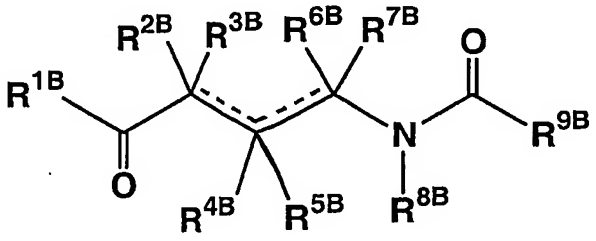
(A)

wherein each symbol has the same meaning as defined in Japanese Patent Laid-Open No. 4-346978, 1- and 3-isomer mixtures thereof, an addition salt with an inorganic or organic acid or base thereof. A specific embodiment comprised by this formula is the compound telmisartan:



Matrix metalloproteinase (hereinafter abbreviated as MMP) is a neutral metalloproteinase having zinc at an active center thereof. Twenty or more molecular species thereof, each having a different primary structure, have been identified to date. MMP decomposes collagen, laminin, proteoglycan, fibronectin, elastin, gelatin or the like, so that it acts on the growth of articular tissues, bone tissues or connective tissues, and the reconstruction of these tissues. However, it is considered that the destruction of various tissues occurring in a pathological condition is caused by an increase in the expression or activity of MMP due to destruction of the function to control MMP.

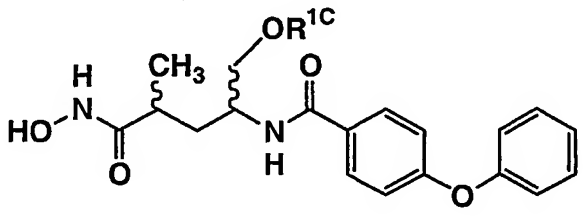
International Publication WO 99/19296 (Patent Document 2) describes, as a compound with an MMP inhibitory action, a compound represented by the following general formula (B):



(B)

wherein each symbol has the same meaning as defined in International Publication WO99/19296.

Moreover, International Publication WO 03/015762 (Patent Document 3) suggests that a compound with an MMP inhibitory activity represented by the general formula (C) set forth below is effective for the treatment of heart failure:



(C)

wherein each symbol has the same meaning as defined in International Publication WO 03/015762.

Presently, there are no agents that can be satisfactorily used for the treatment of heart failure. It is strongly desired that a highly effective pharmaceutical agent be provided.

As a result of intensive studies directed towards finding a potent agent for treating heart failure, the present inventors have found that a pharmaceutical agent comprising an AII receptor antagonist and an MMP inhibitor in combination can achieve the above object, thereby completing the present invention.

That is to say, the present invention relates to the following (1) to (12):

(1) A preventive and/or therapeutic agent for heart failure and/or cardiac hypertrophy, comprising an angiotensin II receptor antagonist and a matrix metalloproteinase inhibitor in combination;

(2) The preventive and/or therapeutic agent according to (1) above, wherein the angiotensin II antagonist is one or more selected from a group consisting of telmisartan, candesartan cilexetil, eprosartan, irbesartan, losartan, pratosartan,

ripisartan, valsartan, zolasartan and olmesartan either alone or in combination with a diuretic such as hydrochlorothiazide;

(3) The preventive and/or therapeutic agent according to (1) above, wherein the matrix metalloproteinase inhibitor is one or more selected from a group consisting of N-hydroxy-5-ethoxymethyloxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)amino-pentane amide, N-hydroxy-5-hydroxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)aminopentane amide, batimastat, marimastat, neovastat, prinomastat, metastat, rebimastat, D-1927, S-3304 and ABT-518;

(4) The preventive and/or therapeutic agent according to (1) above, wherein the angiotensin II antagonist is telmisartan and the matrix metalloproteinase inhibitor is N-hydroxy-5-ethoxymethyloxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)aminopentane amide;

(5) The preventive and/or therapeutic agent according to (1) above, further comprising an HMG-CoA reductase inhibitor in combination;

(6) The preventive and/or therapeutic agent according to (5) above, wherein the HMG-CoA reductase inhibitor is one or more selected from a group consisting of atorvastatin, pravastatin, lovastatin, simvastatin, fluvastatin, serivastatin, bitavastatin, and losvastatin;

(7) The preventive and/or therapeutic agent according to (5) above, wherein the angiotensin II antagonist is telmisartan, the matrix metalloproteinase inhibitor is N-hydroxy-5-ethoxymethyloxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)aminopentane amide, and the HMG-CoA reductase inhibitor is atorvastatin, pravastatin or simvastatin;

(8) The preventive and/or therapeutic agent according to (7) above, wherein the HMG-CoA reductase inhibitor is atorvastatin;

(9) A method for preventing and/or treating heart failure and/or cardiac hypertrophy, characterized by that an effective amount of a pharmaceutical agent comprising an angiotensin II receptor antagonist and a matrix metalloproteinase inhibitor in combination is administered to mammals;

(10) The method according to (9) above, wherein the angiotensin II antagonist is telmisartan and the matrix metalloproteinase inhibitor is N-hydroxy-5-ethoxymethyloxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)aminopentane amide;

(11) A combined use of an angiotensin II receptor antagonist and a matrix metalloproteinase inhibitor for the production of a preventive and/or therapeutic agent for heart failure and/or cardiac hypertrophy; and

(12) The combined use according to (11) above, wherein the angiotensin II antagonist is telmisartan and the matrix metalloproteinase inhibitor is N-hydroxy-5-ethoxymethyloxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)aminopentane amide.

Any type of compound may be used as an AII receptor antagonist or MMP inhibitor in the present invention, as long as it has an AII receptor antagonism or MMP inhibitory action. These compounds include not only the known AII receptor antagonists or MMP inhibitors, but also novel AII receptor antagonists or MMP inhibitors that will be found in the future.

Examples of an AII receptor antagonist used in the present invention may include one or more selected from a group consisting of telmisartan, candesartan cilexetil, eprosartan, irbesartan, losartan, valsartan, zolasartan and olmesartan either alone or in combination with a diuretic such as hydrochlorothiazide. Of these, telmisartan or its salts such as the sodium salt are preferable.

Examples of an MMP inhibitor used in the present invention may include one or more selected from a group consisting of N-hydroxy-5-ethoxymethyloxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)aminopentane amide, N-hydroxy-5-hydroxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)aminopentane amide, batimastat, marimastat, neovastat, prinomastat, metastat, rebimastat, D-1927, S-3304 and ABT-518. Of these, N-hydroxy-5-ethoxymethyloxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)aminopentane amide is preferable.

Of the above MMP inhibitors, N-hydroxy-5-ethoxymethyloxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)aminopentane amide and N-hydroxy-5-hydroxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)aminopentane amide are described in the specification of WO99/19296, for example. Likewise, batimastat is described in the specification of

EP Patent No. 498665, marimastat is described in the specification of GB Patent No. 2268934, neovastat is described in the specification of WO 97/16197, and prinomastat is described in the specification of WO 95/4735.

Examples of an HMG-CoA reductase inhibitor used in the present invention include one or more selected from a group consisting of atorvastatin, pravastatin, lovastatin, simvastatin, fluvastatin, serivastatin, bitavastatin, and losvastatin. Of these, atorvastatin, pravastatin and simvastatin are preferable, and atorvastatin is particularly preferable.

A preventive and/or therapeutic agent for heart failure and/or cardiac hypertrophy comprising telmisartan as an AII receptor antagonist and N-hydroxy-5-ethoxymethyloxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)aminopentane amide as an MMP inhibitor in combination is preferable in the present invention. Moreover, a preventive and/or therapeutic agent for heart failure and/or cardiac hypertrophy comprising telmisartan as an AII receptor antagonist and N-hydroxy-5-ethoxymethyloxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)aminopentane amide as an MMP inhibitor and further comprising atorvastatin, pravastatin or simvastatin as an HMG-CoA reductase inhibitor in combination is also preferable.

It was confirmed that the toxicity of each drug used in the present invention is considerably low, and that the preventive and/or therapeutic agent comprising the drugs in combination is safe enough to be used as a pharmaceutical agent.
In the present invention, the AII receptor antagonist may be combined with the MMP inhibitor, so as to obtain a single pharmaceutical preparation to be administered. Otherwise, these two components may be converted into two different pharmaceutical preparations and administered in combination. That is, the form of a combined administration may also be adopted. This combined administration includes concepts of a simultaneous administration and a time difference administration. Regarding the time difference administration, it may be possible to first administer the AII receptor antagonist and then administer the MMP inhibitor, or it may also be possible to first administer the MMP inhibitor and then the AII receptor

antagonist. Anyway, the administration of two different preparations, that is, the form of a combined administration is preferable.

In a case of comprising AII receptor antagonist with the MMP inhibitor and further comprising the HMG-CoA reductase inhibitor in combination, the same dosage form and administration method as above may be adopted.
When the pharmaceutical agents are used for the purpose of the present invention, the agents may generally be administered systemically or locally, orally or parenterally. Oral administration is preferable.

When the agent is administered for the purpose of the present invention, it may be used as an internal use solid preparation or internal use liquid preparation for oral administration, or as an injection, external medicine, suppository, eye drop or inhalant for parenteral administration.

Examples of an internal use solid preparation for oral administration may include a tablet, a pill, a capsule, a powder, and a granule. Specific examples of a capsule may include a hard capsule and a soft capsule. Specific examples of a tablet may include a sublingual tablet, a buccal tablet, a troche, an oral patch preparation, and an oral disintegrating agent.

In order to prepare these internal use solid preparations, one or more active substances may be directly used, or these substances may be mixed with an excipient (e.g., lactose, mannitol, glucose, microcrystalline cellulose, starch, etc.), a binder (e.g., hydroxypropyl cellulose, polyvinylpyrrolidone, magnesium aluminometasilicate, etc.), a disintegrator (e.g., carboxymethylcellulose calcium, etc.), a lubricant (e.g., magnesium stearate, etc.), a stabilizer, a solubilizer (e.g., glutamic acid, asparatic acid, etc.), or the like. The thus obtained mixture is converted into a pharmaceutical preparation according to a common method. In addition, the obtained pharmaceutical preparation may be coated with a coating agent (saccharose, gelatin, hydroxypropyl cellulose, hydroxypropyl methyl cellulose phthalate, etc.), as necessary. The preparation may also be coated with two or more

layers. Moreover, a capsule of an absorbable substance such as gelatin may also be included herein.

Examples of an internal use liquid preparation for oral administration may include a pharmaceutically acceptable aqueous solution, suspension, emulsion, syrup, and elixir. In order to prepare such a liquid preparation, one or more active substances are dissolved, suspended or emulsified in a commonly used diluent (e.g., purified water, ethanol or a mixed solution thereof, etc.). Moreover, a wetting agent, suspending agent, emulsifier, sweetener, flavor, aromatic, preservative, buffer or the like may also be added to the liquid.

The dosage of the AII receptor antagonist varies depending on drugs to be used as the antagonist. It is preferably used within the range where each used drug is commonly applied. However, for the treatment for diseases of the present invention, the drug may also be administered over the above range. For example, telmisartan is preferably administered orally, and the dosage depends on age, body weight, symptom, therapeutic effects or the like. However, in general, this drug is preferably administered orally once or several times a day at a daily dose of 10 to 160 mg per adult. More preferably, this drug is administered orally once a day at a daily dose of 20, 40, 80 or 120 mg per adult.

The dosage of the MMP inhibitor varies depending on drugs to be used as the inhibitor. It is used within the range where each used drug does not show toxicity and the safety is confirmed. For example, N-hydroxy-5-ethoxymethyloxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)aminopentane amide is preferably administered orally, and the dosage depends on age, body weight, symptom, therapeutic effects or the like. However, this agent is administered orally once or several times a day, generally at a daily dose of 5 to 1,200 mg, and preferably at a daily dose of 12.5 to 600 mg per adult.

The dosage of the HMG-CoA reductase inhibitor varies depending on drugs to be used as the inhibitor. It is preferably used within the range where each used drug is

commonly applied. However, for the treatment for diseases of the present invention, the drug may also be administered over the above range. For example, atorvastatin is preferably administered orally, and the dosage depends on age, body weight, symptom, therapeutic effects or the like. However, in general, this drug is preferably administered orally once or several times a day at a daily dose of 5 to 100 mg per adult. More preferably, this drug is administered orally once a day at a daily dose of 5, 10, 20 or 40 mg per adult. Pravastatin is preferably administered orally, and the dosage depends on age, body weight, symptom, therapeutic effects or the like. However, in general, this drug is preferably administered orally once or several times a day at a daily dose of 5 to 100 mg per adult. More preferably, this drug is administered orally once a day at a daily dose of 5, 10, 20 or 40 mg per adult. Simvastatin is preferably administered from orally, and the dosage depends on age, body weight, symptom, therapeutic effects or the like. However, in general, this drug is preferably administered orally once or several times a day at a daily dose of 5 to 100 mg per adult. More preferably, this drug is administered orally once a day at a daily dose of 5, 10, 20 or 40 mg per adult.

An excellent effect to suppress heart failure and/or cardiac hypertrophy can be obtained by combining an AII receptor antagonist with an MMP inhibitor. Additionally, combining an AII receptor antagonist with an MMP inhibitor favorably affects the treatment or prevention of atherosclerosis, stroke, neuro-inflammatory diseases or nephropathy (diabetic and non-diabetic).

A pharmaceutical agent comprising an AII receptor antagonist either alone or in combination with a diuretic such as hydrochlorothiazide and an MMP inhibitor is useful for the prevention and/or treatment of heart failure and/or cardiac hypertrophy.

Figure 1 shows a cumulative survival rate of Dahl salt-sensitive rats in the case of a single administration of drug a, or a combined administration of drugs a and b.

Figure 2 shows a left ventricular end-diastolic dimension determined by transthoracic echocardiogram.

Figure 3 shows a left ventricular end-systolic dimension determined by transthoracic echocardiogram.

Figure 4 shows a wall stress determined by transthoracic echocardiogram.

The effects of the present invention will be explained with reference to the following experiments. However, the present invention is not limited thereto.

Examples:

Example 1: **Dahl salt-sensitive rat heart failure model**

With regard to test agents, telmisartan (drug a) was used as an AII receptor antagonist, and N-hydroxy-5-ethoxymethyloxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)aminopentane amide (drug b) was used as an MMP inhibitor.

(1) Life prolongation effect

Dahl salt-sensitive rats (16 rats/group) fed with high-salt food were divided into the following 3 groups at the age of 11 weeks after they had developed cardiac hypertrophy. Then, drugs were administered in the following manner:

Group 1: Only drug a (5 mg/kg/day) was administered orally to the rats beginning at the age of 11 weeks.

Group 2: Drug a (5 mg/kg/day) was administered orally to the rats beginning at the age of 11 weeks. Beginning at the age of 15 weeks, drug b (twice a day at 100 mg/kg) was also orally administered in combination.

Control group: 0.5% carboxymethyl cellulose was administered orally to the rats beginning at the age of 11 weeks.

Each of the above administrations was continued until the rats that had developed cardiac hypertrophy died. The survival of the rats in the control group and in the test

agent administration groups was checked during and after the administration, and it was then analyzed by the Kaplan-Meier method, so that the cumulative survival rate was calculated. The results are shown in Figure 1.

(2) Determination of function and morphology of the left heart

Using the above Dahl salt-sensitive rat heart failure models, the left ventricular end-diastolic dimension, left ventricular end-systolic dimension, and wall stress of the rats were determined by transthoracic echocardiogram at the age of 11, 15, 17 and 19 weeks. The results are shown in Figure 2 (left ventricular end-diastolic dimension), Figure 3 (left ventricular end-systolic dimension), and Figure 4 (wall stress).
Group 2 in which drugs a and b were administered in combination in the present model showed a significant life prolongation effect, when compared with the control group and Group 1 in which drug a alone was administered thereto (Figure 1).
Moreover, regarding Group 2 in which drugs a and b were administered in combination to the rats at the age of 17 weeks, both the left ventricular end-diastolic dimension and the left ventricular end-systolic dimension significantly decreased (Figures 2 and 3). Based on these results, it is found that the narrowing of the lumen of the left cardiac ventricle occurred. Furthermore, the wall stress was also decreased (Figure 4). Based on these results, it is determined that the enlargement of the left cardiac ventricle observed during the heart failure period was suppressed by the combined administration of drugs a and b.
Accordingly, it is determined that the combined administration of drugs a and b has an excellent effect upon heart failure and/or cardiac hypertrophy.

Example 2: **Example of pharmaceutical preparation**

The following ingredients were mixed by a common method and then subjected to tablet making, so as to obtain 10,000 tablets, each of which contains 20 mg of telmisartan and 50 mg of N-hydroxy-5-ethoxymethyloxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)aminopentane amide as active ingredients.

• Telmisartan	200 g
• N-hydroxy-5-ethoxymethyloxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)aminopentane amide	500 g
• Carboxymethyl cellulose calcium	100 g
• Magnesium stearate	50 g
• Microcrystalline cellulose	250 g

Claims:

1. A preventive and/or therapeutic agent for heart failure and/or cardiac hypertrophy comprising an angiotensin II receptor antagonist and a matrix metalloproteinase inhibitor in combination.

2. The preventive and/or therapeutic agent according to claim 1, wherein the angiotensin II antagonist is one or more selected from a group consisting of telmisartan, candesartan cilexetil, eprosartan, irbesartan, losartan, pratosartan, ripisartan, valsartan, zolasartan and olmesartan either alone or in combination with a diuretic such as hydrochlorothiazide.

3. The preventive and/or therapeutic agent according to claim 1, wherein the matrix metalloproteinase inhibitor is one or more selected from a group consisting of N-hydroxy-5-ethoxymethyloxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)aminopentane amide, N-hydroxy-5-hydroxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)-aminopentane amide, batimastat, marimastat, neovastat, prinomastat, metastat, rebimastat, D-1927, S-3304 and ABT-518.

4. The preventive and/or therapeutic agent according to claim 1, wherein the angiotensin II antagonist is telmisartan and the matrix metalloproteinase inhibitor is N-hydroxy-5-ethoxymethyloxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)aminopentane amide.

5. The preventive and/or therapeutic agent according to claim 1, further comprising an HMG-CoA reductase inhibitor in combination.

6. The preventive and/or therapeutic agent according to claim 5, wherein the HMG-CoA reductase inhibitor is one or more selected from a group consisting of atorvastatin, pravastatin, lovastatin, simvastatin, fluvastatin, serivastatin, bitavastatin, and losvastatin.

7. The preventive and/or therapeutic agent according to claim 5, wherein the angiotensin II antagonist is telmisartan, the matrix metalloproteinase inhibitor is N-hydroxy-5-ethoxymethyloxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)aminopentane amide, and the HMG-CoA reductase inhibitor is atorvastatin, pravastatin or simvastatin.

8. The preventive and/or therapeutic agent according to claim 7, wherein the HMG-CoA reductase inhibitor is atorvastatin.

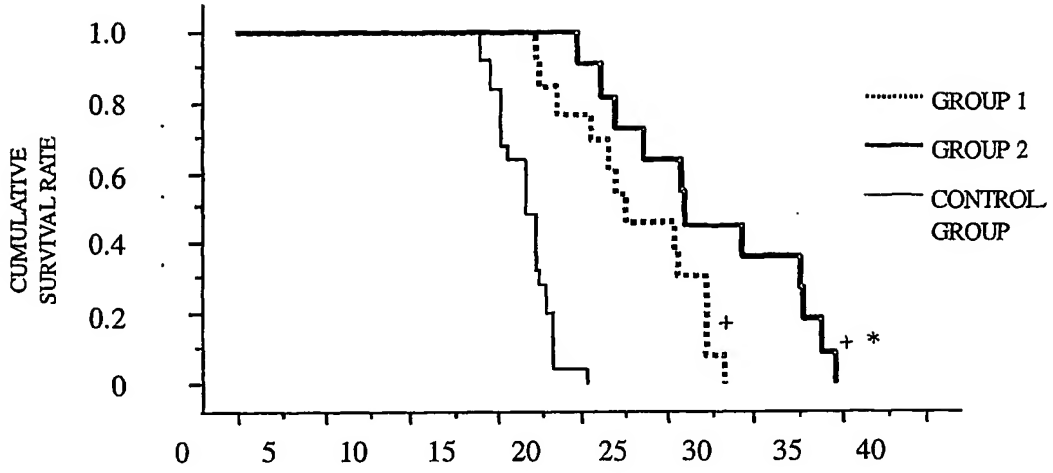
9. A method for preventing and/or treating heart failure and/or cardiac hypertrophy, characterized in that an effective amount of a pharmaceutical agent an angiotensin II receptor antagonist and a matrix metalloproteinase inhibitor in combination is administered to mammals.

10. The method according to claim 9, wherein the angiotensin II antagonist is telmisartan and the matrix metalloproteinase inhibitor is N-hydroxy-5-ethoxymethyloxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)aminopentane amide.

11. A combined use of an angiotensin II receptor antagonist either alone or in combination with a diuretic such as hydrochlorothiazide and a matrix metalloproteinase inhibitor for the production of a preventive and/or therapeutic agent for heart failure and/or cardiac hypertrophy.

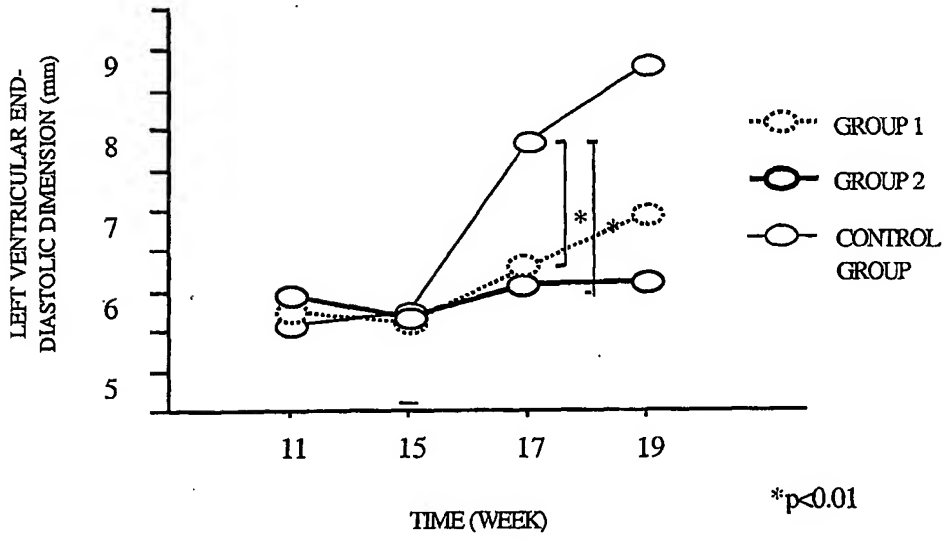
12. The combined use according to claim 11, wherein the angiotensin II antagonist is telmisartan and the matrix metalloproteinase inhibitor is N-hydroxy-5-ethoxymethyloxy-2(S)-methyl-4(S)-(4-phenoxybenzoyl)aminopentane amide.

Figure 1



+P<0.01 vs. CONTROL GROUP
*p<0.05 GROUP 1 vs. GROUP 2

Figure 2



*p<0.01

5

Figure 3

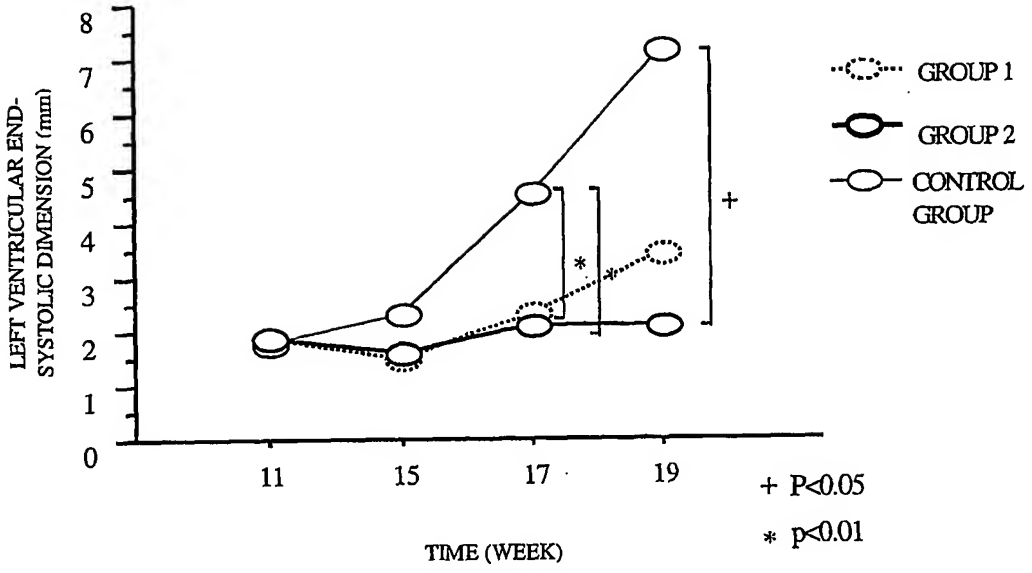


Figure 4